

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
3 June 2004 (03.06.2004)

PCT

(10) International Publication Number
WO 2004/046126 A1

- (51) International Patent Classification⁷: **C07D 311/72**,
C07C 69/017, 69/157
- (21) International Application Number:
PCT/EP2003/010789
- (22) International Filing Date:
29 September 2003 (29.09.2003)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
02025989.1 21 November 2002 (21.11.2002) EP
- (71) Applicant (for all designated States except US): **DSM IP ASSETS B.V.** [NL/NL]; Het Overloon 1, NL-6411 TE Heerlen (NL).
- (72) Inventors; and
(75) Inventors/Applicants (for US only): **BONRATH**, Werner [DE/DE]; Luckenbachweg 29, 79115 Freiburg (DE). **DITTEL**, Claus [DE/CH]; Wengistrasse 29, CH-4500 Solothurn (CH). **NETSCHER**, Thomas [DE/DE]; Am Huligraben 2, 79189 Bad Krozingen (DE). **PABST**, Thomas [DE/DE]; Im Anger 44, 93098 Mintraching (DE). **SCHMID**, Rudolf [CH/CH]; Unterer Rheinweg 44, CH-4057 Basle (CH).
- (74) Agent: **MUELLER**, Ingrid; Roche Vitamins Ltd., Patent Department (VMD), Wurmisweg 576, CH-4303 Kaiseraugst (CH).
- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: **MANUFACTURE OF TOCOPHERYL ACETATE**

(57) **Abstract:** A process for the manufacture of 3-phytyl-2,5,6-trimethylhydroquinone-1-acetate, and optionally therefrom tocopheryl acetate, comprises either C-alkylating 2,3,6-trimethylhydroquinone-1-acetate with isophytol or phytol in the presence of a sulphur(VI) containing catalyst of the formula R^1SO_2OH , wherein R^1 signifies hydroxy, halogen, lower alkyl, halogenated lower alkyl or aryl, in an aprotic organic solvent, or O-alkylating 2,3,6-trimethylhydroquinone-1-acetate with a phytyl halide in a polar aprotic organic solvent in the presence of a base, and subjecting the so-obtained 4-O-phytyl-2,3,6-trimethylhydroquinone-1-acetate to a rearrangement reaction, and in each case optionally submitting the so-obtained 3-phytyl-2,5,6-trimethylhydroquinone-1-acetate to a ring closure reaction to produce tocopheryl acetate. The invention also includes the novel compound 3-phytyl-2,5,6-trimethylhydroquinone-1-acetate and certain stereoisomers thereof, and also the further novel compound 4-hydroxy-2,3,6-trimethyl-5-[3-(4,8,12-trimethyltridecyl)-but-3enyl]phenyl acetate which itself is one of several isomers of 3-phytyl-2,5,6-trimethylhydroquinone-1-acetate formed by isomerization under the influence of heating, e.g. during its distillation as part of the isolation and purification procedure following its manufacture as indicated above. (All-rac)- α -tocopherol, which may be derived from its acetate, is known to be the most active industrially important member of the vitamin E group.